: 10750466

Item Search of Final Prod.

(AJ)

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FILE 'HOME' ENTERED AT 20:20:56 ON 28 JUN 2005

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 20:21:10 ON 28 JUN 2005
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 JUN 2005 HIGHEST RN 853049-67-9
DICTIONARY FILE UPDATES: 27 JUN 2005 HIGHEST RN 853049-67-9

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TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

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* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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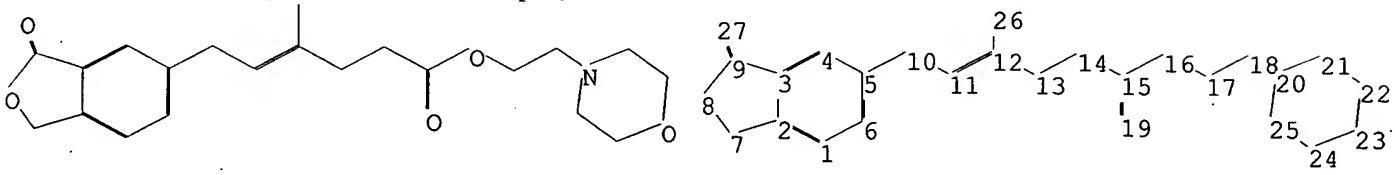
Uploading C:\Program Files\Stnexp\Queries\10750466.str



chain nodes :

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10  11  12  13  14  15  16  17  18  19  26  27
ring nodes :
1  2  3  4  5  6  7  8  9  20  21  22  23  24  25
chain bonds :
5-10  9-27  10-11  11-12  12-13  12-26  13-14  14-15  15-16  15-19  16-17  17-18  18-20
ring bonds :
1-2  1-6  2-3  2-7  3-4  3-9  4-5  5-6  7-8  8-9  20-21  20-25  21-22  22-23  23-24
24-25
exact/norm bonds :
2-7  3-9  7-8  8-9  9-27  15-16  15-19  16-17  18-20  20-21  20-25  21-22  22-23  23-24
24-25
exact bonds :
5-10  10-11  11-12  12-13  12-26  13-14  14-15  17-18
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:CLASS
11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS  18:CLASS  19:CLASS
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L1      STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 20:21:27 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      1 TO ITERATE

100.0% PROCESSED       1 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            1 TO       80
PROJECTED ANSWERS:               1 TO       80

L2            1 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 20:21:32 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     45 TO ITERATE

100.0% PROCESSED      45 ITERATIONS                               38 ANSWERS
SEARCH TIME: 00.00.01

L3           38 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   161.33     161.54

FILE 'CAPLUS' ENTERED AT 20:21:39 ON 28 JUN 2005
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FILE COVERS 1907 - 28 Jun 2005 VOL 143 ISS 1
FILE LAST UPDATED: 27 Jun 2005 (20050627/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> s l3
L4          1632 L3

=> s l3 and (process or make or made or synth? or method)
            1632 L3
         2101905 PROCESS
          211295 MAKE
         1153268 MADE
         2041735 SYNTH?
         2859962 METHOD
L5           274 L3 AND (PROCESS OR MAKE OR MADE OR SYNTH? OR METHOD)

=> s l5 and cataly?
         1255896 CATALY?
L6             8 L5 AND CATALY?

=> d ed abs ibib hitstr 1-8
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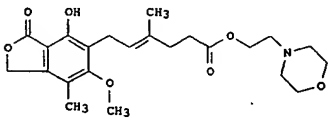
L5 and L?

struct of Intermed.

29 Dec. 2005

L6 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 22 Oct 2004
GI



I

AB 4-[(2-Hydroxyethyl)morpholino] mycophenolate I is prepared by the esterification of mycophenolic acid or its salts with 4-(2-hydroxyethyl)morpholine under microwave irradiation

ACCESSION NUMBER: 2004:876397 CAPLUS
DOCUMENT NUMBER: 141:366238
TITLE: Microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate
INVENTOR(S): Adhikary, Laxmi; Suryanarayan, Shrikumar
PATENT ASSIGNEE(S): Biocon Limited, India
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004089946	A1	20041021	WO 2003-IN143	20030407

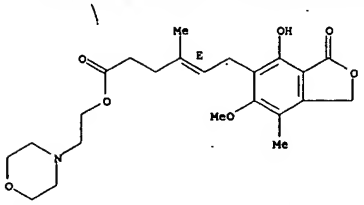
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2003-IN143 20030407
OTHER SOURCE(S): CASREACT 141:366238
IT 128794-94-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(microwave esterification synthesis of 4-[(2-hydroxyethyl)morpholino] mycophenolate)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

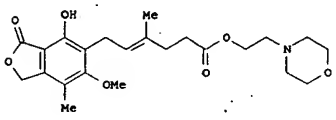
Unavail on East

L6 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

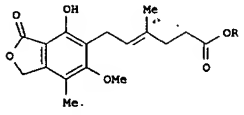


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 27 Aug 2004
GI



I



II

AB A process for making mycophenolate mofetil (I) comprising: conducting a catalytic transesterification by reacting a low-carbon alkyl ester of mycophenolic acid (II; R = Me, Et, Pr, Bu) with 2-morpholinoethanol [4-(2-hydroxyethyl)morpholine] to obtain a crude product of mycophenolate mofetil, which is then isolated and purified.

ACCESSION NUMBER: 2004:701805 CAPLUS
DOCUMENT NUMBER: 141:225522
TITLE: Process for making mycophenolate mofetil by transesterification
INVENTOR(S): Lee, Kwang-chung; Lin, Shu-chuan; Chiu, Ray-hwa
PATENT ASSIGNEE(S): Taiwan
SOURCE: U.S. Pat. Appl. Publ., 3 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

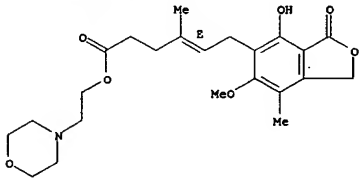
Appl.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004167130	A1	20040826	US 2003-750466	20031229
TW 221414	B1	20041001	TW 2003-92103728	20030221

PRIORITY APPLN. INFO.: TW 2003-92103728 A 20030221
OTHER SOURCE(S): CASREACT 141:225522; MARPAT 141:225522
IT 128794-94-5P, Mycophenolate mofetil
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for preparation of mycophenolate mofetil by transesterification of mycophenolic acid esters with morpholinoethanol)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L6 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L6 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 23 May 2003
AB The present invention relates to an improved method for synthesis of mycophenolate mofetil by reacting mycophenolic acid with an excess of 2-morpholinoethanol using an enzyme as catalyst in a water-free organic solvent and its subsequent purification The use of an anhydrous organic solvent leads to higher conversion of mycophenolic acid. Water generated in the reaction may also be removed using mol. sieves to further improve conversion of mycophenolic acid to mycophenolate mofetil.
ACCESSION NUMBER: 2003:397024 CAPLUS
DOCUMENT NUMBER: 138:384235
TITLE: Enzymatic preparation of mycophenolate mofetil
INVENTOR(S): Patil, Nitin; Mendhe, Rakesh; Khedkar, Anand; Melarkode, Ramakrishnan; Suryanarayan, Shrikumar
PATENT ASSIGNEE(S): Biocon India Limited, India
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

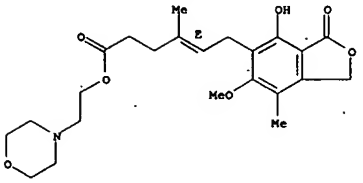
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003042393	A1	20030522	WO 2001-IN202	20011116

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2001-IN202 20011116
OTHER SOURCE(S): CASREACT 138:384235
IT 128794-94-5P, Mycophenolate mofetil
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(enzymic preparation of mycophenolate mofetil)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L6 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

N/A

↑ acid → acid chloride

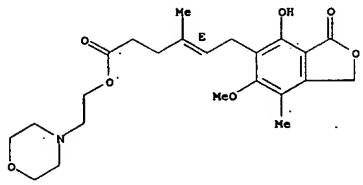
↳ Acid → Product

↳ C_6-C_{12} alkane solvent Chexane

L6 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 06 May 2003
AB A review. Mycophenolic acid (MPA) in its morpholinoester prodrug form, mycophenolate mofetil (MMF; CellCept, Roche) is one of the most promising immunosuppressive drugs recently developed. MPA specifically inhibits IMPDH II. This enzyme catalyses the oxidation of inosine monophosphate to xanthine monophosphate, as an intermediate metabolite in the synthesis of guanosine monophosphate. Two isoforms of human inosine monophosphate dehydrogenase (IMPDH), designed type I and type II, have been identified and sequenced and are 85% conserved at the amino acid level. Type I is constitutively expressed and is the predominant isoform over type II in normal, nonreplicating cells while type II is selectively upregulated in neoplastic and replicating cells, predominating over type I. As a result of this inhibition of IMPDH, the GTP cellular pool is severely depleted (down to 10% of normal levels). However, MPA has been shown to exhibit serious, but not life-threatening, side effects except in very rare cases. Both hematol. and gastrointestinal (GI) adverse events are associated with the use of MPA and MPA-containing agents such as MMF. These adverse events include anemia, nausea, vomiting, diarrhea, gastritis, and ulcers. It has also been reported that in very rare cases an increased risk of opportunistic pathogens can be a serious, life-threatening effect of being on MPA treatment. It is the GI disturbances that this review will discuss; this area will be explored because very little discussion and research in the literature has been done to assess the mechanisms by which GI toxicity is occurring. Phase III clin. trials have clearly shown that the most common GI complications included ulceration of the GI mucosa, esophagitis, and diarrhea. Severe diarrhea in renal transplant recipients has been reported, but due to the complexity in assessing MPA's involvement, the elucidation of how MPA contributes to gastrotoxicity has been poorly studied. While GI effects of MPA have been reported, little has been done to elucidate MPA role in causing GI toxicity. This review will specifically look at IMPDH isoforms that MPA inhibits and the secondary effects from the inhibition of these isoforms.
ACCESSION NUMBER: 2003:343110 CAPLUS
DOCUMENT NUMBER: 140:22435
TITLE: A possible mechanism of gastrointestinal toxicity posed by mycophenolic acid
AUTHOR(S): Neerman, Michael F.; Boothe, Dawn M.
CORPORATE SOURCE: Department of Chemistry, Texas A&M University, College Station, TX, 77845, USA
SOURCE: Pharmacological Research (2003), 47(6), 523-526
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
IT 128794-94-5, Mycophenolate Mofetil
RL: ADV (Adverse effect, including toxicity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(possible mechanism of gastrointestinal toxicity posed by mycophenolic acid)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L6 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

N/A

— RS122.P45

L6 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 01 Mar 2001

AB A review with 25 refs. Mycophenolate mofetil (MMF, CellCept), a semisynthetic derivative of mycophenolic acid (MPA) produced by a fungus, is an inhibitor of the inosine monophosphate dehydrogenase (IMPDH) enzyme (IC50 = 25 nM) that catalyzes the synthesis of guanosine monophosphate (GMP) from inosine. GMP is an essential nucleoside for purine synthesis during cell division. As T and B-lymphocytes almost exclusively use the de novo pathway of purine synthesis, these cells are particularly sensitive to the inhibitory action of MMF. It has a mechanism of action distinct from cyclosporine and tacrolimus. Although MMF does not affect cytokine production, by inhibiting the rate-limiting enzyme IMPDH in the de novo synthesis of purines, it inhibits the proliferation of T and B-lymphocytes, the production of antibodies, and the generation of cytotoxic T lymphocytes. Reversal of acute allograft rejection and increased survival of kidney, heart and bone marrow cell allograft has been shown in several animal studies. Moreover, it was suggested that MMF combined with CsA prevented the acute rejection, and approx. half of the animals became long-term survivors. The Ministry of Health and Welfare approved MMF in 1999 for use for rejection treatment in renal transplantation based on several prospective, randomized and blind efficacy trials.

ACCESSION NUMBER: 2001:149197 CAPLUS
DOCUMENT NUMBER: 134:172618
TITLE: Pharmacological profiles of mycophenolate mofetil (CellCept), a new immunosuppressive agent
AUTHOR(S): Yashima, Yukihiko; Ohgane, Tohru
CORPORATE SOURCE: Nippon Roche Res. Cent., Nippon Roche K. K., 200, Kajiwara, Kamakura city, Kanagawa, 247-8530, Japan
SOURCE: Nippon Yakurigaku Zasshi (2001), 117(2), 131-137
CODEN: NYKZAU; ISSN: 0015-5691
PUBLISHER: Nippon Yakuri Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

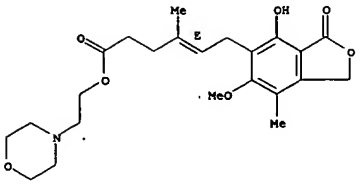
IT 116680-01-4, CellCept
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. profiles of mycophenolate mofetil (CellCept), a new immunosuppressive agent)

RN 116680-01-4 CAPLUS

CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, hydrochloride, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L6 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



● HCl

L6 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 16 Jun 2000

AB Methods for the manufacture of mycophenolate are disclosed. Mycophenolate mofetil is biochem. synthesized using mycophenolic acid and 2-morpholinoethanol with the help of an enzyme. Mycophenolate mofetil is also chemical synthesized non-catalytically by refluxing mycophenolic acid with 2-morpholinoethanol in the absence of a third solvent or a catalyst.

ACCESSION NUMBER: 2000:402025 CAPLUS
DOCUMENT NUMBER: 133:29685
TITLE: Methods of producing esters of mycophenolate
INVENTOR(S): Sircar, Anindya; Khedkar, Anand; Kulkarni, Madhav; Suryanarayan, Shrikumar; Sridharan, Madhavan; Acharaya, Poorpanapranja; Samvasivam, Ganesh
PATENT ASSIGNEE(S): Biocon India Limited, India
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000034503	A2	20000615	WO 1999-IN70	19991209
WO 2000034503	A3	20000817		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IN 188985	A	20021130	IN 1998-MA2754	19981209
CA 2354554	AA	20000615	CA 1999-2354554	19991209
EP 1137795	A2	20011004	EP 1999-964770	19991209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6709846	B1	20040323	US 2001-857579	20010607
PRIORITY APPLN. INFO.:			IN 1998-MA2754 A	19981209
			WO 1999-IN70 W	19991209

OTHER SOURCE(S): CASREACT 133:29685

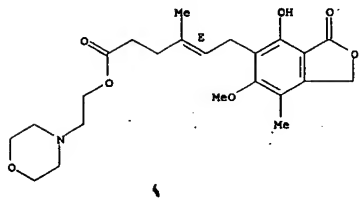
IT 128794-94-5P, Mycophenolate mofetil
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); IMF (Industrial manufacture); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(producing esters of mycophenolate)

RN 128794-94-5 CAPLUS

CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L6 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

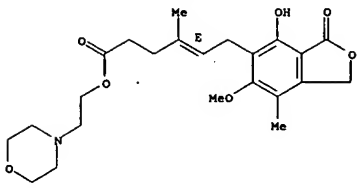


→ uses the acid

L6 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 24 Apr 2000
AB Mycophenolate mofetil (MMF) is an effective immunosuppressant developed for use in organ transplantation. It specifically targets lymphocyte purine biosynthesis. However, side effects do occur. Understanding how the active metabolite of MMF, mycophenolic acid (MPA) affects the normally integrated interaction between intracellular purine and pyrimidine pathways might aid the development of improved therapeutic regimes. We used a primary human T-lymphocyte model to study how preincubation with MPA (0.1-50 μM) affected normal ribonucleotide pool responses to phytohemagglutinin using radiolabeled precursors. MPA not only restricted the mitogen-induced expansion of GTP pools, but actually induced a severe drop in both GTP (10% of unstimulated cells) and GDP-sugar pools, with a concomitant fall in ATP (up to 50%). These effects were concentration dependent.
By contrast, uridine pools expanded whereas CTP pools remained at resting levels. These changes were confirmed by the altered incorporation of [14C]-bicarbonate and [14C]-glycine into nucleotides. Restriction of [14C]-hypoxanthine incorporation and reduction of [14C]-uridine uptake comparable to that of unstimulated cells indicated that MPA also inhibited both salvage routes of nucleotide synthesis. MPA affects pyrimidine as well as purine responses to mitogens in T-lymphocytes, but not in an integrated way. The mol. mechanisms underlying these disproportionate changes can best be explained by MPA-related inhibition of amidophosphoribosyltransferase, catalyzing the first step in purine biosynthesis. This would increase phosphoribosylpyrophosphate availability, thereby stimulating UTP biosynthesis. Such imbalances, coupled with ATP-depletion, could underlie reported side effects and might be overcome by appropriate combination therapies.
ACCESSION NUMBER: 2000:264361 CAPLUS
DOCUMENT NUMBER: 133:276031
TITLE: Mycophenolic acid-induced GTP depletion also affects ATP and pyrimidine synthesis in mitogen-stimulated primary human T-lymphocytes
AUTHOR(S): Qiu, Ying; Fairbanks, Lynette D.; Ruckemann, Katarzyna; Hawrylowicz, Catherine M.; Richards, David F.; Kirschbaum, Bernhard; Simmonds, H. Anne
CORPORATE SOURCE: Purine Research, Guy's Hospital, London, SE1 9RT, UK
SOURCE: Transplantation (2000), 69(5), 890-897
CODEN: TRPLAU; ISSN: 0041-1337
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 128794-94-5, Mycophenolate mofetil
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MPA-induced GTP depletion also affects ATP and pyrimidine synthesis in mitogen-stimulated primary human T-lymphocytes)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L6 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

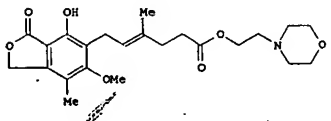


REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

NA

RD 120.7.T65

L6 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 08 Jan 1994
GI



I

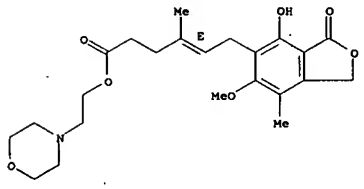
AB A process for the esterification of mycophenolic acid with 2-morpholinoethanol in an inert organic solvent (e.g., toluene/xylene) capable of azeotropic removal of water gave product, the immunosuppressive drug mycophenolate mofetil (I). Yields were 78-83%. Inclusion of an acid or base catalyst in the reaction gave no increase in either completion or yield, and is thus unnecessary. Addnl. solvents are benzene, mineral spirits, and CH_2Cl_2.
ACCESSION NUMBER: 1994:8601 CAPLUS
DOCUMENT NUMBER: 120:8601
TITLE: Direct esterification of mycophenolic acid
INVENTOR(S): Knox, Martin; Donegan, Gregory; Smith, Dennis A.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA
SOURCE: U.S., 6 pp. Cont.-in-part of U.S. Ser. No. 911,635, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5247083	A	19930921	US 1992-993146	19921218
WO 9401427	A1	19940120	WO 1993-US6390	19930709
W: JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 649422	A1	19950426	EP 1993-917003	19930709
EP 649422	B1	19970319		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08500340	T2	19961116	JP 1994-503484	19930709
JP 3199741	B2	20010820		
AT 150460	E	19970415	AT 1993-917003	19930709
ES 2098763	T3	19970501	ES 1993-917003	19930709
PRIORITY APPLN. INFO.:			US 1992-911635	B2 19920710
			US 1992-993146	A 19921218
			WO 1993-US6390	W 19930709

OTHER SOURCE(S): CASREACT 120:8601
IT 128794-94-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, by direct esterification)
RN 128794-94-5 CAPLUS
CN 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (4E)- (9CI) (CA INDEX NAME)

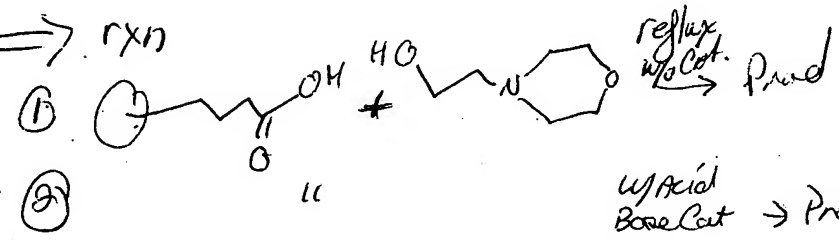
Double bond geometry as shown.

L6 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



General esterification rxn.
Rejected: Morrison & Boyd "Organic Chem" 3rd Ed. pp. 841-43, 72-74

→ Ref in Spec (p.1)



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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	52.21	213.75

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-5.84	-5.84

STN INTERNATIONAL LOGOFF AT 20:23:43 ON 28 JUN 2005